Supplementary Material

1. Supplementary Movie Legends

2. Supplementary Tables

3. Consortium

Supplementary Movie legends

Video S1. In the context of severe spastic tetrapleagia with generalized hypotonia, patient 7 presents clonic jerks of upper and lower limbs exacerbated by tactile and visual stimulation, associated with eye blinking and roving eye movements. Diffuse muscle wasting and intention tremor can also be observed.

Video S2. Patient 9 displays spastic tetraplegia with evident muscle wasting. He has both horizontal and rotatory nystagmus. Despite the profound psychomotor delay, social smiling after tactile stimulation is present.

Video S3. Patient 11 suffers from severe generalized hypotonia with complete lack of head control. He has poor response to visual stimulation and bilateral constant divergent strabismus.

Table S1 Summary of the clinical features of *TRAPPC4* patients homozygous for the recurrent c.454+3 A>G variant (NM_016146.5).

Families	I		II	III		IV	V		VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI			XVII	Van Bergen *et al*, 2020	Kaur *et al*, 2020
Ancestry	EGY		EGY	EGY		IRN	IRN		EGY	EGY	EGY	PRT	IRN	AUS	USA	USA	USA	USA	EGY			EGY		
Individuals	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20	Pt 21	Pt 22	Pt 23	7 pts	1 pt
	III-2	III-3	III-5	III-1	V-2	III-4	IV-3	V-1	V-2	III-5	II-3	II-3	II-1	III-4	II-1	III-2	II-2	II-2	II-1	II-1	II-2	II-3	II-3	(3 families)†	(IND)
Current age	N/A	7 y	N/A	N/A	N/A	N/A	1.9 y	N/A	5 y	1 y	3.6 y	5.2 y	7 y	N/A	8 y	5.9 y	8y	3 y	8y	N/A	9y	2.6y	3.6y	Mean alive at 8.8y	1.6 y
(sex)	(F)	(M)	(M)	(M)	(M)	(F)	(M)	(F)	(M)	(F)	(M)	(M)	(F)	(F)	(M)	(M)	(M)	(F)	(F)	(F)	(F)	(M)	(F)	(3F-1M)	(F)
Age of death	8y	Alive	Alive	5y	Alive	18y	Alive	6y	Alive	Alive	Alive	Alive	Alive	7y	Alive	Alive	Alive	Alive	Alive	6y	Alive	Alive	Alive	Mean 4.2 y	Alive
cause	Inf	-	-	Inf	-	Inf	-	N/A	-	-	-	-	-	N/A	-	-	-	-	-	N/A	N/A	N/A	-	(2F-1M)	-
Consanguinity	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	-	-	-	+	+	+	+	3	-
Pregnancy	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	Reg	HTN	Reg	Reg	Oligo	Reg	Reg	IVF	Reg	Reg (7)	Reg
Congenital MC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+ -2SD	-	-	-	-	-	-	-	-	- (3 N/A)	N/A
Dysmorphism	+	+	-	-	-	+	+	+	+	-	+	+	+	-	-	-	+	-	+	-	-	-	+	7	+
Feeding difficulties	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ (6), 1 N/A	+
Development																									
Motor	Abs	Abs	Abs	Abs	N/A	Abs	Abs	Abs	Abs	Abs	Delay	Abs	Abs	Delay	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Severely delayed (7)	Abs
Speech	Abs	Abs	Abs	Abs	N/A	Abs	Abs	Abs	Abs	Abs	Delay	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs	Abs		Abs
Social	Abs	Abs	Abs	Abs	N/A	Abs	Abs	Abs	Smile	Abs	Delay	Abs	Abs	Delay	N/A	Abs	Abs	Abs	Smile	Abs	Abs	Abs	Abs		Abs
Regression	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+ (3), 4 N/A	No
Profound ID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(7)	+
Progressive MC	+	+	+	+	N/A	+	+	N/A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SDS	-8.5	-6.5	-8.8	-6.8		-7	-5.3		-6.9	-5	-5.4	-6.2	-9.3	-5.6	-6	-3.2	-3.6	-5	-5.2	-5.6	-6.2	-6	-6.2	(-4.3 to -7)	(-6 to -8)
Seizures																								(+7)	
Onset	3 mo	6 mo	3 mo	6 mo	N/A	6 mo	3 mo	3 mo	5 mo	6 mo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3 mo	6m	6m	4m	4m	6m	3-12 mo	N/A
Type	AS, FS	FS	FS	TS, FS	N/A	TCS	TCS	N/A	TCS	TS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IS	IS	MS	MS,FS	TS	MS, FS	GM, GS, FS,	N/A
Frequency	1/weeks	1/weeks	1/weeks	1/mo	N/A	2-3/mo	5-6/day	N/A	clusters	Daily	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2/week	every several days	every several days	several weeks	clusters	clusters	N/A
Refractory	-	-	-	-	N/A	-	-	N/A	+	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	+	+	-	fairly controlled	+/-	N/A
Abnormal EEG	+	+	+	+	N/A	N/A	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	-
Hypotonia	+	-	-	-	-	+	N/A	N/A	-	-	-	-	-	-	-	+	-	+	+	-	-	-	-	+(5)	N/A
Spastic tetraplegia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(7)	+
Hyperreflexia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ (3), 4 N/A	N/A
Movement disorder	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	+	-	+	-	+	+	+	+	+(5)	+
Vision	Imp	Imp	Imp	Imp	Imp	N/A	Imp	Imp	-	Imp	Imp	N/A	Imp	Cat	CVI	Ny	Imp	CVI	No pursuit	NT	NT	Mild follow	NT	2 CVI, 1 OA	CVI
Hearing loss	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+ (2), 1 N/A	-
Muscle wasting	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+	+	+	+	-	-
Biochemical abnormalities	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	↑lactate	N/A	N/A	N/A	N/A	-	↑CK, lactate, SGOT, SGPT
Brain MRI																								4/7	
Cerebal atrophy	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(4)	+
White matter dz	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(4)	+
Ventriculomegaly	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(4)	+
BS hypoplasia	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	N/A	+
CB atrophy	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+(3)	+
CCH	+	+	+	+	+	N/A	N/A	N/A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+(1)	+

Abbreviations. Abs= Absent; AS = atonic seizures; AUS = Australia; BS = brainstem; Cat= Cataract; CB = cerebellar; CCH = corpus callosum hypoplasia; CK, creatine kinase; CVI = cortical visual impairment; EEG = electroencephalogram; F = female; FS = focal seizures; GM = grand mal; GS = gelastic seizures; HTN = hypertension; ID = intellectual disability; Imp= Impaired; IND= Indian; Inf = infection; IS = infantile spasms; M = male; MC = microcephaly; mo = months; MS= myoclonic seizures; N/A = not available; NN= none noted; NT= No tracking; Ny = nystagmus; OA = optic atrophy; Oligo= Oligohydramnios; Prof = profound; PRT= Portugal; Pt = patient; Reg= regular; SDS = standard deviations; TS = tonic seizures; TCS = tonic-clonic seizures; USA = United States of America; y = years. † Caucasian, Turkish, and French-Canadian. ‡ Including plasma lactate, creatine phosphokinase, and serum glutamic oxaloacetic transaminase (SGOT) and pyruvic transaminase (SGPT). Regression was defined as the clear loss of milestones during aging, and included motor, coordination and social milestones. The present cases are compared with the cases presented in Van Bergen et al. and Kaur et al. in the two right-most columns. Van Bergen presented 7 patients from 3 families. Numbers in parentheses represent the number of patients displaying the feature if available.

Table S2. TRAPP subunit subcomplex components and clinical syndrome so far associated with disease. Most TRAPP subunits are part of both TRAPPII and III complexes except for C10, which is exclusively part of TRAPPCII, and TRAPPC11 ,-12, and -13, which are exclusively part of TRAPPIII. All conditions are autosomal recessive except the *TRAPPC2* gene which is X-linked.

Subunit	Complex	Clinical Condition	OMIM#
C1	II and III		
C2	II and III	Spondyloepiphyseal dysplasia tarda, X-linked	313400
C2L	II and III	Encephalopathy, progressive, early-onset, with episodic rhabdomyolysis	618331
C3	II and III		
C4	II and III	Neurodevelopmental disorder with epilepsy, spasticity, and brain atrophy	618741
C5	II and III		
C6A	II and III		
C6B	II and III	Neurodevelopmental disorder with microcephaly, epilepsy, and brain atrophy	617862
C9	II and III	Mental retardation, autosomal recessive 13	613192
C10	II		
C11	III	Muscular dystrophy, limb-girdle, autosomal recessive 18	615356
C12	III	Encephalopathy, progressive, early-onset, with brain atrophy and spasticity	617669
C13	III		

Members of the Undiagnosed Diseases Network Consortium

Maria T. Acosta, Margaret Adam, David R. Adams, Pankaj B. Agrawal, Mercedes E. Alejandro, Justin Alvey, Laura Amendola, Ashley Andrews, Euan A. Ashley, Mahshid S. Azamian, Carlos A. Bacino, Guney Bademci, Eva Baker, Ashok Balasubramanyam, Dustin Baldridge, Jim Bale, Michael Bamshad, Deborah Barbouth, Pinar Bayrak-Toydemir, Anita Beck, Alan H. Beggs, Edward Behrens, Gill Bejerano, Jimmy Bennet, Beverly Berg-Rood, Jonathan A. Bernstein, Gerard T. Berry, Anna Bican, Stephanie Bivona, Elizabeth Blue, John Bohnsack, Carsten Bonnenmann, Devon Bonner, Lorenzo Botto, Brenna Boyd, Lauren C. Briere, Elly Brokamp, Gabrielle Brown, Elizabeth A. Burke, Lindsay C. Burrage, Manish J. Butte, Peter Byers, William E. Byrd, John Carey, Olveen Carrasquillo, Ta Chen Peter Chang, Sirisak Chanprasert, Hsiao-Tuan Chao, Gary D. Clark, Terra R. Coakley, Laurel A. Cobban, Joy D. Cogan, Matthew Coggins, F. Sessions Cole, Heather A. Colley, Cynthia M. Cooper, Heidi Cope, William J. Craigen, Andrew B. Crouse, Michael Cunningham, Precilla D'Souza, Hongzheng Dai, Surendra Dasari, Mariska Davids, Jyoti G. Dayal, Matthew Deardorff, Esteban C. Dell'Angelica, Shweta U. Dhar, Katrina Dipple, Daniel Doherty, Naghmeh Dorrani, Emilie D. Douine, David D. Draper, Laura Duncan, Dawn Earl, David J. Eckstein, Lisa T. Emrick, Christine M. Eng, Cecilia Esteves, Tyra Estwick, Marni Falk, Liliana Fernandez, Carlos Ferreira, Elizabeth L. Fieg, Laurie C. Findley, Paul G. Fisher, Brent L. Fogel, Irman Forghani, Laure Fresard, William A. Gahl, Ian Glass, Rena A. Godfrey, Katie Golden-Grant, Alica M. Goldman, David B. Goldstein, Alana Grajewski, Catherine A. Groden, Andrea L. Gropman, Irma Gutierrez, Sihoun Hahn, Rizwan Hamid, Neil A. Hanchard, Kelly Hassey, Nichole Hayes, Frances High, Anne Hing, Fuki M. Hisama, Ingrid A. Holm, Jason Hom, Martha Horike-Pyne, Alden Huang, Yong Huang, Rosario Isasi, Fariha Jamal, Gail P. Jarvik, Jeffrey Jarvik, Suman Jayadev, Jean M. Johnston, Lefkothea Karaviti, Emily G. Kelley, Jennifer Kennedy, Dana Kiley, Isaac S. Kohane, Jennefer N. Kohler, Deborah Krakow, Donna M. Krasnewich, Elijah Kravets, Susan Korrick, Mary Koziura, Joel B. Krier, Seema R. Lalani, Byron Lam, Christina Lam, Brendan C. Lanpher, Ian R. Lanza, C. Christopher Lau, Kimberly LeBlanc, Brendan H. Lee, Hane Lee, Roy Levitt, Richard A. Lewis, Sharyn A. Lincoln, Pengfei Liu, Xue Zhong Liu, Nicola Longo, Sandra K. Loo, Joseph Loscalzo, Richard L. Maas, Ellen F. Macnamara, Calum A. MacRae, Valerie V. Maduro, Marta M. Majcherska, May Christine V. Malicdan, Laura A. Mamounas, Teri A. Manolio, Rong Mao, Kenneth Maravilla, Thomas C. Markello, Ronit Marom, Gabor Marth, Beth A. Martin, Martin G. Martin, Julian A. Martínez-Agosto, Shruti Marwaha, Jacob McCauley, Allyn McConkie-Rosell, Colleen E. McCormack, Alexa T. McCray, Elisabeth McGee, Heather Mefford, J. Lawrence Merritt, Matthew Might, Ghayda Mirzaa, Eva Morava, Paolo M. Moretti ,Marie Morimoto, John J. Mulvihill, David R. Murdock, Mariko Nakano-Okuno, Avi Nath, Stan F. Nelson, John H. Newman, Sarah K. Nicholas, Deborah Nickerson, Donna Novacic, Devin Oglesbee, James P. Orengo, Laura Pace, Stephen Pak, J. Carl Pallais, Christina GS. Palmer, Jeanette C. Papp, Neil H. Parker, John A. Phillips III, Jennifer E. Posey, Lorraine Potocki, Barbara N. Pusey, Aaron Quinlan, Wendy Raskind, Archana N. Raja, Deepak A. Rao, Genecee Renteria, Chloe M. Reuter, Lynette Rives, Amy K. Robertson, Lance H. Rodan, Jill A. Rosenfeld, Natalie Rosenwasser, Maura Ruzhnikov, Ralph Sacco, Jacinda B. Sampson, Susan L. Samson, Mario Saporta, C. Ron Scott, Judy Schaechter, Timothy Schedl, Kelly Schoch, Daryl A. Scott, Prashant Sharma, Vandana Shashi, Jimann Shin, Rebecca Signer, Catherine H. Sillari, Edwin K. Silverman, Janet S. Sinsheimer, Kathy Sisco, Edward C. Smith, Kevin S. Smith, Emily Solem, Lilianna Solnica-Krezel, Rebecca C. Spillmann, Joan M. Stoler, Nicholas Stong,

Jennifer A. Sullivan, Kathleen Sullivan, Angela Sun, Shirley Sutton, David A. Sweetser, Virginia Sybert, Holly K. Tabor, Cecelia P. Tamburro, Queenie K.-G. Tan, Mustafa Tekin, Fred Telischi, Willa Thorson, Cynthia J. Tifft, Camilo Toro, Alyssa A. Tran, Brianna M. Tucker, Tiina K. Urv, Adeline Vanderver, Matt Velinder, Dave Viskochil, Tiphanie P. Vogel, Colleen E. Wahl, Stephanie Wallace, Nicole M. Walley, Chris A. Walsh, Melissa Walker, Jennifer Wambach, Jijun Wan, Lee-kai Wang, Michael F. Wangler, Patricia A. Ward, Daniel Wegner, Mark Wener, Tara Wenger, Katherine Wesseling Perry, Monte Westerfield, Matthew T. Wheeler, Jordan Whitlock, Lynne A. Wolfe, Jeremy D. Woods, Shinya Yamamoto, John Yang, Guoyun Yu, Diane B. Zastrow, Chunli Zhao, Stephan Zuchner